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An Unexplained Case of Progressive Spastic Paraparesis in an Individual with Known DiGeorge Syndrome

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Abstract
DiGeorge syndrome (22q11.2 deletion) is associated with several neurologic disorders including structural abnormalities involving brain and spine, movement disorders, and epilepsy. Progressive spastic paraparesis has not been reported with DiGeorge syndrome. We report an individual in which DiGeorge syndrome was associated with progressive spastic paraparesis. This report extends the clinical phenotype of DiGeorge syndrome and presents the differential diagnosis of progressive spastic paraparesis in individuals with DiGeorge syndrome which provides insight into the clinical evaluation of such individuals.

Introduction

First described in 1965, DiGeorge syndrome is the result of a deletion on chromosome 22 at 22q11.2 involving the *TBX1* gene, which disrupts embryonic development of the third and fourth pharyngeal arches. Specifically, *TBX1* is considered to be the critical gene associated with the majority of features associated with 22q11.2 deletion syndrome [1, 2]. The incidence of 22q11.2 deletion syndrome is approximately 1 in 3,000 to 1 in 6,000 live births and 90–95% are de novo [2]. Initial descriptions of DiGeorge syndrome included thymic hypoplasia,

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hypocalcemia, cardiac defects, and dysmorphic facies [3]. Subsequently, the phenotype has been expanded variably to include autoimmune disease, intellectual disability, psychiatric disorders, and skeletal, renal, gastrointestinal, and genitourinary abnormalities [2].

Multiple neurologic conditions are associated with DiGeorge syndrome. General neurologic deficits include decreased truncal stability, hypotonia, increased tendon reflexes, and clonus. Brain and spine malformations include decreased brain volume, polymicrogyria, gray matter heterotopia, and tethered cord. Movement disorders include early onset Parkinsonism as well as difficulties with balance and coordination. The risk of developing epilepsy is increased in subjects with DiGeorge syndrome. As noted above, DiGeorge syndrome may be associated with neuropsychiatric disorders including intellectual disability, anxiety, autism spectrum disorders, attention deficit hyperactivity disorder, schizophrenia, and dementia [4].

Case Presentation

Following a complicated gestation (mother unable to recall exact nature of complications) and uneventful delivery, this individual underwent ligation of her patent ductus arteriosus to repair a perimembranous ventricular septal defect in infancy. She required constant hospitalizations for upper respiratory infections as a child but had normal attainment of neurodevelopmental milestones. Mild cognitive impairment became evident around third grade, requiring special education classes. At age 16, she developed progressive gait disturbance. Symptoms consistent with myoclonic seizures led to treatment with clonazepam. A diagnosis of spinocerebellar ataxia was entertained. She graduated from high school. In her 20s, her recurrent upper respiratory infections were thought to be due to hypogammaglobulinemia, for which she was treated with recurrent infusions of intravenous immunoglobulin. She was also noted to have chronic hypocalcemia.

She came under our care at age 33, at which point her neurological examination showed marked, bilaterally symmetric, lower extremity hyperreflexia, spasticity, weakness; slight ataxia in the upper extremities; and extensor plantar reflexes. She was not able to stand. Extraocular movements and speech were normal. At this point, the individual was felt to have a slow progressive spastic paraparesis syndrome of unknown etiology and the focus remained on symptom management for several years. At age 40, she began experiencing a decline in proximal strength and cognition. Her neurologic exam at this point revealed marked weakness in the lower extremities with fairly good power in the arms. Sensation was minimally reduced in the legs to vibration and proprioception and light touch distally. Muscle stretch reflexes were pathologically hyperactive at the knees with clonus but absent ankle jerks. Muscle stretch reflexes were mildly hyperactive in the arms and at the jaw. She did not have spastic speech or a pseudobulbar affect. She had prominent extensor plantar responses bilaterally.

Urostomy and colostomy were performed at age 37 to treat neurogenic bladder and chronic diarrhea. Chronic somatic pain complaints which underwent extensive evaluation and diagnostics were also a constant feature of her presentation.

Given the absence of obvious cerebellar signs that would be consistent with spinocerebellar ataxia, several other possibilities were explored. Evaluation of B_{12} deficiency, vitamin E deficiency, thyroid dysfunction, zinc disturbance, copper deficiency, copper excess, arsenic excess, lead excess, mercury excess, and NMO antibodies all failed to reveal a specific cause. Oxysterols, lysosomal enzymes, cholestanol, and very-long-chain fatty acids were also tested and were within normal ranges. Her lumbar puncture results were within normal limits

including normal IgG and no oligoclonal bands. Human T-cell lymphotropic virus I/II testing was negative.

Genetic testing included specific testing for Friedreich ataxia, which revealed one FXN gene with a full expansion of 1,200 GAA repeats. The other allele was normal with 13 GAA repeats. Further mitochondrial genome analysis and mitochondrial nuclear gene testing identified a heterozygous 2.6 Mb deletion at 22q11.2 including both the HIRA (TUPLE) and TBX1 genes, consistent with a diagnosis of 22q11.2 microdeletion syndrome or DiGeorge syndrome. This diagnosis was felt to explain her history of cardiac defects, hypocalcemia, and hypogammaglobulinemia. However, the 22q11.2 deletion was not felt to explain all of her neurologic symptoms. Whole exome sequencing (WES) (GeneDX, USA) was performed, which did not find any additional pathogenic variants associated with the reported phenotype or a point mutation in her second FXN gene. WES also did not identify any changes in genes associated with hereditary spastic paraparesis.

Her brain MRI at 42 years of age indicated nonspecific areas of signal abnormality within the periventricular and subcortical white matter. This was slightly increased in comparison to an MRI at 33 years of age, but without callosal and pericallosal disease commonly seen in multiple sclerosis. There was a chronic right frontal periventricular lacunar infarction without evidence of superimposed acute infarction. An MRI of her entire spine at 33 and 38 years of age showed a small spinal cord without any signal abnormality. An MRI of her lumbar spine at 41 years of age showed diffuse muscle atrophy. Finally, an MRI of her cervical spine at 42 years of age showed multilevel cervical spondylosis.

EEGs performed at ages 36, 38, 42, and 44 years of age were normal.

Neuropsychological testing performed at 43 years of age revealed impaired function across nearly all cognitive domains including memory, attention, visuo-construction, psychomotor speed, and executive functions, thought to be consistent with major neurocognitive disorder. Her premorbid IQ was determined to be 73 using the Wechsler Test of Adult Reading, indicating borderline to mild cognitive impairment.

Finally, EMGs were performed at 41 and 44 years of age on the more symptomatic left lower extremity. Examination was limited by the patient being unable to transfer from her wheelchair and wishing to remain in her chair for the test. Motor nerve conduction studies revealed a low amplitude peroneal response with normal latency and conduction velocity. Sensory nerve conduction study showed no response. Limited needle examination due to patient's wheelchair dependence revealed mildly large motor unit potentials and irritability of the medial gastrocnemius. Deltoid muscle was normal. The results supported the diagnosis of axonal polyneuropathy with no indication of myopathy.

Conclusion

Here, we present a case of a 45-year-old woman with genetically confirmed DiGeorge syndrome and progressively worsening spastic paraparesis of unknown etiology. Mitochondrial disease, copper deficiency, vitamin deficiency, heavy metal excess, multiple sclerosis, adrenomyeloneuropathy, cerebrotendinous xanthomatosis, Niemann-Pick disease, Friedreich ataxia and neuromyelitis optica were ruled out. Imaging, lumbar puncture, EMG, and genetic testing also failed to reveal a specific cause. Thus, we propose that her neurologic manifestations are related to DiGeorge syndrome and, to our knowledge, this is a unique finding not previously described in the literature.

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Statement of Ethics

The authors have no ethical conflicts to disclose. Written informed consent for patient information to be published was provided by both the patient and her mother. The research was conducted ethically in accordance with the World Medical Association Declaration of Helsinki.

Disclosure Statement

The authors have no conflicts of interest to declare.

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Author Contributions

R.D. collected the information, performed literature search, and drafted the manuscript. K.P., J.K.F., and R.M.P. supervised the work, performed significant manuscript revisions, and gave final approval for publication.

References

1 Hopkins SE, Chadehumbe M, Crowley TB, Zackai EH, Bilaniuk LT, Mcdonald-Mcginn DM. Neurologic challenges in 22q11.2 deletion syndrome. Am J Med Genet A. 2018 Oct;176(10):2140–5.
2 Mcdonald-Mcginn DM, Sullivan KE, Marino B, Philip N, Swillen A, Vorstman JAS, et al. 22q11.2 deletion syndrome. Nat Rev Dis Primers. 2015 Nov;1:15071.
3 Wilson DI, Burn J, Scambler P, Goodship J. DiGeorge syndrome: part of CATCH 22. J Med Genet. 1993 Jul;30(10):852–6.
4 Kobrynski LJ, Sullivan KE. Velocardiofacial syndrome, DiGeorge syndrome: the chromosome 22q11.2 deletion syndromes. Lancet. 2007;370(9596):1443–52.